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(FILE 'HOME' ENTERED AT 16:31:32 ON 15 FEB 2006)

FILE 'MEDLINE, SCISEARCH, CAPLUS, BIOSIS' ENTERED AT 16:31:43 ON 15 FEB 2006

L1 16081 S LENTIVIR?
L2 330659 S ARTHRITIS
L3 14398 S IRAP OR IL1RA OR (INTERLEUKIN(5W)RECEPTOR(5W)ANTAGONIST)
L4 9 S L1(L)L2(L)L3
L5 5 DUP REM L4 (4 DUPLICATES REMOVED)
L6 5 SORT L5 PY

=> d ti so au ab pi l6 1-5

L6 ANSWER 1 OF 5 SCISEARCH COPYRIGHT (c) 2006 The Thomson Corporation on STN
TI Gene therapy for rheumatoid arthritis
SO EXPERT OPINION ON BIOLOGICAL THERAPY, (NOV 2001) Vol. 1, No. 6, pp. 971-978.
ISSN: 1471-2598.
AU Gouze E; Ghivizzani S C; Palmer G D; Gouze J N; Robbins P D; Evans C H (Reprint)
AB Rheumatoid arthritis (RA) is a disabling, painful disorder affecting 1% of the world's population. Although the aetiology of RA remains unknown, recent advances in understanding its pathophysiology have led to the characterisation of several proteins whose activities may be anti-arthritic. Clinical application of such proteins has greatly improved the treatment of RA, but the disease remains incurable and difficult to manage in a substantial number of patients. Thus, there are continued efforts to develop new therapeutic strategies. Because RA is a chronic condition, effective treatment will probably require the presence of therapeutic agents for extended periods of time. In the case of proteins, this is problematic. Gene therapy may offer a solution to this problem. Experimental studies have confirmed the feasibility, efficacy and safety of gene therapy for the treatment of animal models of arthritis. Several different approaches have shown promise in this regard, including gene transfer to the synovial lining cells of individual joints and the systemic delivery of genes to extra.:articular locations. One unexpected finding has been the 'contralateral effect' in which gene delivery to one joint of an ani mal with polyarticular disease leads to improvement of multiple joints. Investigation of this phenomenon has led to interest in cell trafficking and the genetic modification of antigen-presenting cells (APC). The first Phase I clinical trial tested the feasibility and safety of ex vivo gene transfer to the synovial lining of human joints. This clinical trial has been successfully completed and two other Phase I trials are in progress. A Phase 11 study is now being planned to investigate the efficacy of gene transfer to the joints of patients with early stage RA.

L6 ANSWER 2 OF 5 MEDLINE on STN
TI In vivo gene delivery to synovium by lentiviral vectors.
SO Molecular therapy : journal of the American Society of Gene Therapy, (2002 Apr) 5 (4) 397-404.
Journal code: 100890581. ISSN: 1525-0016.
AU Gouze Elvire; Pawliuk Robert; Pilapil Carmencita; Gouze Jean-Noel; Fleet Christina; Palmer Glyn D; Evans Christopher H; Leboulch Philippe; Ghivizzani Steven C
AB The delivery of anti-arthritic genes to the synovial lining of joints is being explored as a strategy for the treatment of rheumatoid **arthritis**. In this study, we have investigated the use of VSV-G pseudotyped, HIV-1-based **lentiviral** vectors for gene delivery to articular tissues. Recombinant **lentivirus** containing a beta-galactosidase/neomycin resistance fusion gene under control of the

elongation factor (EF) 1alpha promoter efficiently transduced human and rat synoviocytes and chondrocytes in cell culture. When directly injected into the knees of rats, this vector transduced synovial lining cells, but not other articular tissues such as cartilage. We also constructed a **lentiviral** vector containing the human **interleukin**-1 **receptor antagonist** (**IL1RA**) cDNA and examined transgene expression in vitro and in vivo following injection into the knee joints of rats. In immunocompetent animals, intra-articular **IL1RA** expression was high and persisted, at a sharply declining rate, for approximately 20 days. In immunocompromised rats, however, **lentivirus**-mediated intra-articular expression of human **IL1RA** was found to persist for at least 6 weeks. Extra-articular expression of the transgene was minimal. These results indicate that **lentiviral** vectors are capable of efficient in vivo gene transfer to synovium and merit further investigation as a means of providing long-term expression for gene-based treatments of **arthritis**.

L6 ANSWER 3 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI Method of treating arthritis using lentiviral vectors in gene therapy
SO PCT Int. Appl., 51 pp.
CODEN: PIXXD2
IN Pawliuk, Robert; Leboulch, Philippe
AB Novel methods for treating and preventing arthritis, such as rheumatoid arthritis, are disclosed which employ lentiviral gene delivery vectors, including HIV-based lentiviral vectors, to deliver a therapeutic gene to a subject. Lentiviral-based vectors treat arthritis by promoting high-level expression of the transferred therapeutic gene in the target tissue of the subject. High-titer VSV-G pseudotyped HIV-1-based lentiviral vectors were evaluated for their ability to deliver exogenous genes to articular tissues. Expression of hIL-1Ra via lentiviral injection reduced inflammation of the knee (site of injection) in arthritis induced rats compared to control animals.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2002083080	A2	20021024	WO 2002-US8600	20020319
WO 2002083080	A3	20030220		
WO 2002083080	C2	20030703		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

L6 ANSWER 4 OF 5 CAPLUS COPYRIGHT 2006 ACS on STN
TI Method of treating arthritis using lentiviral vectors in gene therapy
SO PCT Int. Appl., 54 pp.
CODEN: PIXXD2
IN Pawliuk, Robert; Leboulch, Philippe
AB Novel methods for treating and preventing arthritis, such as rheumatoid arthritis, are disclosed which employ lentiviral gene delivery vectors, including HIV-based lentiviral vectors, to deliver a therapeutic gene to a subject. Lentiviral-based vectors treat arthritis by promoting high-level expression of the transferred therapeutic gene in the target tissue of the subject. High-titer VSV-G pseudotyped HIV-1-based lentiviral vectors were evaluated for their ability to deliver exogenous genes to articular tissues. Expression of hIL-1Ra via lentiviral injection reduced inflammation of the knee (site of injection) in arthritis induced rats compared to control animals.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

PI	WO 2002082908	A1	20021024	WO 2002-US8711 20020321
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
	US 2004241141	A1	20041202	US 2003-688780 20031015

L6 ANSWER 5 OF 5 MEDLINE on STN

TI Lentiviral-mediated gene delivery to synovium: potent intra-articular expression with amplification by inflammation.

SO Molecular therapy : journal of the American Society of Gene Therapy, (2003 Apr) 7 (4) 460-6.
Journal code: 100890581. ISSN: 1525-0016.

AU Gouze Elvire; Pawliuk Robert; Gouze Jean-Noel; Pilapil Carmencita; Fleet Christina; Palmer Glyn D; Evans Christopher H; Leboulch Philippe; Ghivizzani Steven C

AB Clinical translation of gene-based therapies for **arthritis** could be accelerated by vectors capable of efficient intra-articular gene delivery and long-term transgene expression. Previously, we have shown that **lentiviral** vectors transduce rat synovium efficiently in vivo. Here, we evaluated the functional capacity of transgene expression provided by **lentiviral**-mediated gene delivery to the joint. To do this, we measured the ability of a **lentiviral** vector containing the cDNA for human **interleukin**-1 **receptor antagonist** (LV-hIL-1Ra) to suppress intra-articular responses to IL-1beta. Groups of rats were injected in one knee with 5 x 10(7) infectious units of LV-IL-1Ra. After 24 h, a range of doses of fibroblasts (3 x 10(3), 10(4), 3 x 10(4), or 10(5) cells) genetically modified to overexpress IL-1beta was injected into both knees. Intra-articular delivery of LV-hIL-1Ra strongly prevented swelling in all treated knees, even in those receiving the greatest dose of IL-1beta(+) cells. Cellular infiltration, cartilage erosion, and invasiveness of inflamed synovium were effectively prevented in LV-hIL-1Ra-treated knees and were significantly inhibited in contralateral joints. Beneficial effects were also observed systemically in the **lentivirus** -treated animals. Interestingly, intra-articular expression of the IL-1Ra transgene was found to increase in relation to the number of IL-1beta(+) cells injected. Further experiments using GFP suggest this is due to the proliferation of cells, stably modified by the integrative **lentivirus**, in response to inflammatory stimulation.